IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT : Dwek et al.

SERIAL NO. : 10/758,247 EXAMINER: Daniel M. Sullivan, Ph.D.

FILED : January 15, 2004 ART UNIT: 1636

FOR : THERAPEUTIC COMPOSITIONS AND METHODS OF TREATING GLYCOPLIPID STORAGE RELATED DISORDERS

DECLARATION OF OLIVIER H. MORAND

I, Olivier H. Morand, hereby declare that:

1. I am a citizen of France and reside at Unterer Rheinweg 56, 4057, Basel, Switzerland.

2. I received a Ph.D. degree in Nutrition and a Ph.D. degree in Biology & Genetics in 1980 and 1985, respectively, from University of Paris VII, Paris, France. I was a member of the faculty of the Department of Neurochemistry, INSERM, Paris, France from September 1981 until October 1985. From November 1985 until December 1988, I have been a Research Associate in the Department of Biochemistry at the University of Wisconsin, Madison, WI, USA. The details of my education and professional history are set forth in my curriculum vitae, attached hereto as Exhibit A.

3. I have over 25 years experience in the field of lipid biochemistry, my particular area of expertise being in lipid metabolic disorders.

4. I am the author or co-author of more than 30 scientific articles on the subjects of lipid biochemistry. A list of these articles is set forth in my curriculum vitae, attached hereto. My current area of research involves clinical research in inherited defects of lipid metabolism.

5. I am familiar with the subject matter disclosed and claimed in United States Patent Application Number 10/758,247 (hereinafter the '247 application). I am an employee of Actelion Pharmaceuticals, Ltd., to which the present application is to be assigned.

Statements Regarding the Defects of the Aerts et al. Application

6. I have read and am familiar with the Official Action dated February 27, 2007, received in connection with the '247 application. I understand the nature of the rejections made by the Examiner concerning the Aerts et al. application (WO 98/02161, published 22 January 1998) and Platt et al. 1998; IDS AF).

7. The Examiner indicates that the claims are allegedly anticipated by Platt et al. to the extent that they read on the method practiced with NB-DGJ. In light of the amendments to the claims, which are directed to a combination of NB-DNJ and glucocerebrosidase, Platt et al. no longer anticipates the instant claims.

8. The Examiner offers that Aerts et al. demonstrates that N-butyl-deoxynojirimycin is a more than 1,000-fold more potent inhibitor of glucosylceramidase than glucocerebrosidase in *in vitro* experiments and that inhibition of glucosylceramidase can be achieved in intact cells using butyldeoxynojirimycin with no significant inhibition of glucocerebrosidase. The Examiner, therefore, concludes that "Aerts et al. demonstrates that agents such as NB-DNJ are sufficiently selective for glucosylceramidase over glucocerebrosidase that they can be used together". It is my view that the Aerts et al. disclosure would not in fact lead a skilled person to use NB-DNJ and glucocerebrosidase as suggested by the Examiner. My reasoning for this is as follows:

Firstly, it is submitted that Aerts et al. does not teach the combination of NB-DNJ with glucocerebrosidase to treat a glycolipid storage-related disorder. Indeed, Aerts et al. teaches the use of a new family of deoxynojirimycin (DNJ) derivatives as glucosylceramidase inhibitors, which family is characterized in that the DNJ derivatives are substituted on the nitrogen by a large hydrophobic moiety linked to said nitrogen through a spacer. Moreover, this family contains dozens if not hundreds of compounds, since the length of the spacer as well as the nature of the large hydrophobic moiety can both vary. Said new family is set forth throughout the application in marked contrast to "the presently available inhibitors of glucosylceramide synthase" (see p. 9, lines 4-5) and the "known glucosidase inhibitors" (see p. 14, line 31 through to page 15, line 21), the latter obviously including NB-DNJ (see p. 14, line 33) and having had "negative results" (see p. 15, line 19). Therefore, a skilled artisan reading Aerts et al. would not

consider that it discloses the combination of NB-DNJ with glucocerebrosidase because:

- this specific combination is nowhere specifically mentioned in Aerts et al.; and
- NB-DNJ is not part of the invention described in Aerts et al. The invention is exclusively directed to the generation of novel inhibitors that, unlike the known inhibitors (including NB-DNJ), possess functional properties that potentially lend these compounds to use in combination with glucocerebrosidase.

Secondly, NB-DNJ was by far not the only and not the best compound that one skilled in the art would actually have considered when thinking of a combination involving glucocerebrosidase for reducing accumulation of glucosylceramide-containing lipids in a patient afflicted with a glycolipid storage-related disorder.

With regard to the number of glucosylceramidase inhibitors available at the time, the size of this genus of functionally linked molecules/compounds is extremely large. A partial list of glucosylceramidase inhibitors available at the time is presented below:

- 1-phenyl-decanoylamino-3-morpholino-1-propanol (PDMP)
- 1-phenyl-2-hexadecanoylamino-3-morpholino-1-propanol (PPMP)
- butyl-deoxynojirimycin
- butyl-deoxygalactonojirimycin
- D-gluconolacton
- castanospermine
- deoxynojirimycin
- the novel family of DNJ derivatives of Aerts et al., which are substituted on the nitrogen by a large hydrophobic moiety linked to the nitrogen through a spacer

It is obvious, based on this partial list, that structural commonalities that link all of these diverse types of molecules/compounds are absent. Thus, there would be no way to predict which of this spectrum of glucosylceramidase inhibitors might be effective in combination therapy. In light of the above, it would require excessive and undue experimentation for one of skill in the art to test each of the known glucosylceramidase inhibitors in combination with glucocerebrosidase to determine which of these inhibitors would be beneficial in combination with enzyme

replacement therapy. The genus of glucosylceramidase inhibitors is, therefore, not enabled by the Aerts et al. application.

With regard to whether or not NB-DNJ would be viewed as a useful agent for combination with glucocerebrosidase, the literature is essentially universal with respect to the consensus that NB-DNJ is contraindicated under circumstances in which glucocerebrosidase therapy is contemplated. Platt et al. (*J. Biol. Chem.* (1994), **269**(43), 27108-27114; IDS Ref. AR) noticed that "NB-DGJ exhibits fewer complicating enzyme inhibitory characteristics than α- and β-glucosidase inhibitors and may provide a preferable alternative to NB-DNJ for the potential therapeutic treatment of Gaucher's disease and other glycolipid storage disorders" (see p. 27114, bottom of col. 1). This view is strengthened further in a review by Platt and Butters (*Trends in Glycoscience and Glycotechnology* (1995), **7**(38), 495-511) which states that "the lack of effect of NB-DGJ on glucocerebrosidase makes it an attractive drug for adjunctive therapy with Ceredase, the commercial glucocerebrosidase product currently used to treat type I Gaucher patients" (see p. 509, section O, 4th sentence). See also Aerts et al., page 9, lines 1-21; and page 14, line 31 through to page 15, line 17.

Furthermore, the skilled artisan knew that a good indicator for successful treatment of Gaucher disease, one of the glycolipid storage-related disorders, is the chitotriosidase secretion level: the lower that level, the better Gaucher disease is treated. When looking at Table 5 of Aerts et al., one can see that, in order to obtain about 30% reduction of the chitotriosidase secretion level, a concentration of 5 μM NB-DNJ is required whereas a concentration of 0.05 nM of compound p21 is required. In other words, p21 is about 100,000-fold more potent than NB-DNJ in reducing chitotriosidase secretion. Thus, the skilled artisan could only conclude that NB-DNJ was presented as a reference example showing the prior art and its insufficiencies. Indeed, this point is reiterated throughout the document. After having read Aerts et al., a skilled artisan would not have considered NB-DNJ as a viable option for the treatment of glycolipid storage-related disorders, and would therefore definitely have chosen another class of imino sugar derivatives (especially the compound p21 or a closely related analog of that compound) for a combination involving glucocerebrosidase for reducing accumulation of glucosylceramide-containing lipids in a patient affected with a glycolipid storage-related disorder.

In summary, in view of the existing literature taken together with the Aerts et al. document (WO 98/02161), the skilled artisan would not have chosen NB-DNJ as second component of a combination involving glucocerebrosidase for the treatment of a glycolipid storage-related disorder, because:

- based on the literature, the artisan was aware that NB-DNJ had serious side effects, including: inhibition of lysosomal glucocerebrosidase and α-glucosidase I activity, inhibition of the synthesis of more complex glycosphingolipids, and induction of the synthesis of glucosylceramide synthase, which in turn, increases the load on glucosylceramide. Moreover, a skilled artisan would have recognized that NB-DGJ, due to its selectivity, was more interesting than NB-DNJ because NB-DGJ was at least as active as NB-DNJ but would feature fewer side-effects; and
- more importantly, there were much more interesting compounds provided in Aerts et al., i.e., the compound p21 and its analogs, which the skilled artisan could select for a combination with glucocerebrosidase.

As a result, the fact that NB-DNJ combined with glucocerebrosidase gave the surprising results shown in Example 2 of the patent application would certainly not have been anticipated by any of the literature references available or obvious to the skilled artisan at the time when the present patent application was filed since, as mentioned above, the prior art was teaching away from combining NB-DNJ with glucocerebrosidase to treat a glycolipid storage-related disorder.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the above-referenced application or any patent issued thereon.

17th August 2007
DATE

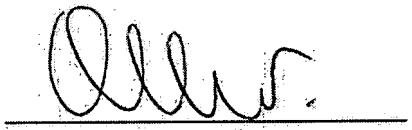
Olivier H. Morand

EXHIBIT A

Curriculum Vitae

Olivier H. Morand

Personal Born on the May 15th, 1954 in New York, U.S.A.
French national

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EDUCATION AND TRAINING

2004-05	Program for Executive Development (IMD, Lausanne)
2002	Global Training for Mobilizing Leaders (IMD, Lausanne)
2000	Training in Leadership and Teamwork (IMD, Lausanne)
1997	Training in Management and Leadership Development (Roche, Basel)
1985	Doctorat d'Etat ès Sciences (Biology and Genetics, University Paris VII)
1980	Doctorat de 3ème Cycle (Nutrition, University Paris VI)
1977	Diplôme d'Etude Approfondie (Nutrition, University Paris VI)
1976	Maîtrise de Biologie Animale (University Paris VI)

CAREER HISTORY

Apr 03-Present Director, Global Life Cycle Leader, Life Cycle Management
Actelion Pharmaceuticals Ltd., Allschwil, Switzerland
- Leading cross-functional Global Life Cycle Team (Zavesca)
- Responsible for clinical trial budget (2005, CHF 12 mio.)
- Member of Global Brand Team (Zavesca)

Oct 89-Mar 03 Department of Metabolic and Vascular Disease Research (formally Department of Cardiovascular Disease Research), Pharmaceuticals Division, F. Hoffmann-La Roche Ltd., Basel, Switzerland
- Scientific Expert (= Vice-Director rank), Departmental Peer-Review Committee member and Project Leader (Jan 02-Mar 03)
- Scientific Specialist and Project Leader (Jan 98-Dec 01)
- Senior Scientist and Project Leader (Oct 93-Dec 97)
- Head of laboratory (Oct 89-Sep 93)

Jan 89-Sep 89 Visiting Scientist
Merck, Sharp and Dohme, Division of Biochemistry (Prof. C.H.R. Raetz), Rahway, New Jersey, U.S.A.

Nov 85-Dec 88 Research Associate
Department of Biochemistry (Prof. C.H.R. Raetz), University of Wisconsin, Madison, Wisconsin, U.S.A.

Sep 81-Oct 85 Chargé de Recherche
INSERM U134, Department of Neurochemistry (Dr. N. Baumann), Hôpital de la Pitié-Salpétrière, Paris, France

Jan 80-Aug 81 Post-doctoral Fellow with Prof. S. Gatt

- Department of Biochemistry, Hadassah Medical School, The Hebrew University, Jerusalem, Israel
- Dept. Human Genetics, Mount Sinai School of Medicine, New York, NY, USA

Oct 77-Dec 79 PhD research work perfomed at INSERM U134, Department of Neurochemistry (Dr. J.M. Bourre), Hôpital de la Pitié-Salpétrière, Paris, France

ADDITIONAL INFORMATION

Languages

- French (mother language)
- English (fluent)
- German (basic)

Computing

- MacIntosh and PC
- Word, Excel, MS-Project, FileMaker, PowerPoint, DeltaGraph, StatView, ISISDraw, ChemDraw, Netscape, Explorer, Outlook, etc.

[August 2007]

LIST OF PUBLICATIONS

PEER-REVIEWED ARTICLES

Treiber A., Morand O. and Clozel M. (2007) The pharmacokinetics and tissue distribution of the glucosylceramide synthase inhibitor miglustat in the rat. Xenobiotica 37, 298–314.

Telford D.E., Lipson S.M., Barrett P.H., Sutherland B.G., Edwards J.Y., Aebi J.D., Dehmlow H., Morand O.H. and Huff M.W. (2005) A novel inhibitor of oxidosqualene:lanosterol cyclase inhibits very low-density lipoprotein apolipoprotein B100 (apoB100) production and enhances low-density lipoprotein apoB100 catabolism through marked reduction in hepatic cholesterol content. Arterioscler. Thromb. Vasc. Biol. 25, 2608-2614.

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Rowe A.H., Argmann C.A., Edwards J.Y., Sawyez C.G., Morand O.H., Hegele R.A. and Huff M.W. (2003) Enhanced synthesis of the oxysterol 24(S),25-epoxycholesterol in macrophages by inhibitors of 2,3-oxidosqualene:lanosterol cyclase: a novel mechanism for the attenuation of foam cell formation. Circ. Res. 93, 717-725.

Dehmlow H., Aebi J.D., Jolidon S., Ji Y.H., von der Mark E.M., Himber J. and Morand O.H. (2003) Synthesis and structure-activity studies of novel orally active non-terpenoic 2,3-oxidosqualene cyclase inhibitors. J. Med. Chem. 46, 3354-3370.

Lenhart A., Reinert D.J., Aebi J.D., Dehmlow H., Morand O.H. and Schulz G.E. (2003) Binding structures and potencies of oxidosqualene cyclase inhibitors with the homologous squalene-hopene cyclase. J. Med. Chem. 46, 2083-2092.

Paulhe F., Perret B., Chap H., Iberg N., Morand O. and Racaud-Sultan C. Phosphoinositide 3-kinase C2α is activated upon smooth muscle cell migration and regulated by $\alpha v\beta 3$ integrin engagement (2002) Biochem. Biophys. Res. Comm. 297, 261-266.

Paulhe F., Racaud-Sultan C., Ragab A., Albiges-Rizo C., Chap H., Iberg N., Morand O. and Perret B. (2001) Differential regulation of phosphoinositide metabolism by $\alpha v\beta 3$ and $\alpha v\beta 5$ integrins upon smooth muscle cell migration. J. Biol. Chem. 276, 41832-41840.

Peffley D.M., Gayen A.K. and Morand O.H. (1998) Downregulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase mRNA levels and synthesis in syrian hamster C100 cells by the oxidosqualene cyclase inhibitor [4'-(6-allyl-ethyl-amino-hexyloxy)-2'-fluoro-phenyl]-(4-bromophenyl)-methanone (Ro 48-8071): comparison to simvastatin. Biochem. Pharmacol. 56, 439-449.

Van der Kooij M., von der Mark E., Kruij J.K., van Velzen A., van Berkel T.J.C. and Morand O.H. (1997) Human monocyte-derived macrophages express a ~120-kD Ox-LDL binding protein with strong identity to CD68. Arterioscler. Thromb. Vasc. Biol. 17, 3107-3116.

Morand O.H., Aebi J., Dehmlow H., Ji Y.H., Gains N., Lengsfeld H. and Himber J. (1997) Ro 48-8071, a new 2,3-oxidosqualene:lanosterol cyclase inhibitor lowering plasma cholesterol in hamsters, squirrel monkeys and minipigs: comparison to simvastatin. J. Lipid Res. 38, 373-390.

Van der Kooij M., Morand O.H., Kempen H.J., and van Berkel T.J.C. (1996) Decrease in scavenger receptor expression in human monocyte-derived macrophages treated with Granulocyte-Macrophage Colony-Stimulating Factor. Arterioscler. Thromb. Vasc. Biol. 16, 106-114.

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Morand O.H., Zoeller R.A. and Raetz C.R.H. (1988) Disappearance of plasmalogens from membranes of animal cells subjected to photosensitized oxidation. J. Biol. Chem. 263, 11597-11606.

Zoeller R.A., Morand O.H. and Raetz C.R.H. (1988) A possible role for plasmalogens in protecting animal cell membranes against photosensitized killing. J. Biol. Chem. 263, 11590-11596.

Morand O., Carré J.B., Homayoun P., Niel E., Baumann N. and Bourre J.M. (1987) Arachidonoyl-Coenzyme A synthetase and non-specific acyl-Coenzyme A synthetase activities in purified rat brain microvessels. J. Neurochem. 48, 1150-1156.

Fibach E., Morand O. and Gatt S. (1986) Photosensitization to UV-irradiation and selective killing of cells following uptake of pyrene-containing fatty acid. J. Cell Sci. 85, 149-159.

Morand O. and Aigrot M.S. (1985) Transport of fatty acids across the membrane of human erythrocyte ghosts. Biochim. Biophys. Acta 835, 68-76.

Morand O., Fibach E., Livni N. and Gatt S. (1984) Induction of lipid storage in cultured leukemic myeloid cells by pyrene-dodecanoic acid. Biochim. Biophys. Acta 793, 95-104.

Morand O., Fibach E. and Gatt S. (1982) Effects of albumin, low temperature and inhibitors of metabolism on transport of fatty acids into cultured human leukemic myeloid cells. Biochim. Biophys. Acta 693, 143-150.

Morand O., Fibach E., Dagan A. and Gatt S. (1982) Transport of fluorescent derivatives of fatty acids into cultured human leukemic myeloid cells and their subsequent metabolic utilization. Biochim. Biophys. Acta 711, 539-550.

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CONTRIBUTIONS TO BOOKS

Morand O.H. (1994) Reactivity of plasmalogens to singlet oxygen and radicals. Methods in Enzymol. Vol. 234, part D, pp.603-620.

Morand O. and Aigrot M.S. (1987) A model for studying membrane fatty acid transport: acyl-Coenzyme A synthesis in human erythrocyte ghosts. In: Enzymes of Lipid Metabolism (Eds: Freysz, Dreyfus, Massarelli and Gatt). Plenum Press. A. Life Sciences. Vol. 116, pp. 437-449.

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Bourre J.M., Morand O., Dumont O., Boutry J.M. and Hauw J.J. (1980) Lipid metabolism and uptake of fatty acids by Schwann cells in culture (in normal and Trembler). In: Neurological Mutations Affecting Myelination. Ed. N.Baumann. Elsevier. pp. 447-452.

PATENTS

Aebi J., Dehmlow H., Himber J., Ji Y-H., Lengsfeld H., Märki H-P., Morand O., Schmid G. Aminoalkyl-substituierte benzo-heterocyclische Verbindungen, Swiss Patent Application No 3480/95, Priority date: 08-12-95.

Aebi J., Guerry P., Jolidon S. and Morand O. (1994)
Verwendung von Phenalkylaminen zur Herstellung von cholesterinsenkenden Arzneimitteln. European Patent # EP 0 636 367 A1, Published 19950201, Granted 20000329.
Method of lowering cholesterol. US patent No. 5574071.
Compound useful for lowering cholesterol. US patent No. 5637771.

Aebi J., Dehmlow H., Himber J., Ji Y-H., Jolidon S., Lengsfeld H., Morand O., Schmid G. Tertiary amines having antimycotic and cholesterol lowering activity. EP0778264 B1, Application No. EP96118872 EP, Filed 19961126, A1, Published 19970611, Granted 20010711.
Tertiary amines. US patents Nos. 6034275 and 6441177.

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Analine derivatives as OSC inhibitors. US patent No. 6683201.

Dehmlow H., Aebi J., Ackermann J., Blum D., Chucholowski A., Morand O., Von der Mark E., Wallbaum S., Weller Th. Novel Aminocyclohexane Derivatives. WO0214267 A1, Application No. EP0109174 EP, Filed 20010808, A1 Published 20020221.
2,3-oxidosqualene-lanosterol cyclase inhibitors. US patent No. 6858651.

Ackermann J., Aebi J., Chucholowski A., Dehmlow H., Morand O., Wallbaum S., Weller Th. Novel Piperidine Derivatives. Application No. EP0109941 EP, Filed 20010829, A1 Published 20020314.

Aebi J., Ackermann J., Dehmlow H., Maerki H.P. Morand O. Cholesterol lowering benzo-thiophenes and benzo-isothioazoles. WO0236584 A1, Application No. EP0112451 EP, Filed 20011026, A1 Published 20020510.
Heteroaromate OSC inhibitors. US patents Nos. 6951879 and 7173043.

INVITED SPEAKER

Morand O. (1994) Oxidosqualene cyclase inhibitors and lipid lowering. Mini-Symposium on Oxidosqualene Cyclase. Organizer: Prof. L. Cattel. Department of Pharmacy, University of Turin, Italy.

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Morand O. (1985) Transport of fatty acids across plasma membranes. NATO-CNRS Research Workshop on "Enzymes of Lipid Metabolism". Strasbourg, France.

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Morand O.H., Aebi J., Guerry P., Hartman P.G., Hennes U., Himber J., Ji Y.H., Jolidon S. and Lengsfeld H. (1994) Potent inhibitors of mammalian 2,3-oxidosqualene lanosterol cyclase are orally active cholesterol lowering agents. Xth International Symposium on Atherosclerosis. Montreal, Canada.

Van der Kooij M., van Berkel T.J.C. and Morand O.H. (1994) Differential effects of GM-CSF on the binding of 125I-Ac-LDL and 125I-Ox-LDL to human monocyte-derived macrophages. VIIIth International Symposium on the Biology of Vascular Cells. Heidelberg, Germany.

Morand O.H., Zoeller R.A. and Raetz C.R.H. (1987) A role for plasmalogens in protecting animal cell membranes against photodynamic damage. NATO-INSERM Advanced Research Workshop on "Lipid Storage Disorders: Biological and Medical Aspects". Toulouse, France.

Morand O.,H. Zoeller R.A. and Raetz C.R.H. (1987) Specific decomposition of plasmalogens linked to the release of activated oxygen in the membrane of cultured Chinese Hamster Ovary cells. The Gordon Research Conference on "Lipid Metabolism". Meriden, New-Hampshire, USA.

Zoeller R.A., Morand O.H. and Raetz C.R.H. (1987) A role for plasmalogens in protecting animal cell membranes against photodynamic damage. Meeting of the American Society for Biological Chemistry. Philadelphia, USA.

Morand O. and Aigrot M.S. (1985) Membrane fatty acid translocation and activation in human erythrocyte ghosts: selective and competitive inhibition by fluorescent polycyclic analogs. The Gordon Research Conference on "Lipid Metabolism". Meriden, New-Hampshire, USA.

Carré J.B., Morand O., Homayoun P., Roux F., Baumann N. and Bourre J.M. (1985) Occurrence of sphingomyelinase activity at pH 7.4 and pH 5.0 in purified rat brain capillaries. Xth Meeting of the International Society for Neurochemistry. Riva del Garda, Italy.

Morand O., Carré J.B., Homayoun P., Niel E., Baumann N. and Bourre J.M. (1985) Arachidonoyl-CoA synthetase and non-specific acyl-CoA synthetase activities in purified rat brain capillaries. Xth Meeting of the International Society for Neurochemistry. Riva del Garda, Italy.

Youcef-Khodja S., Morand O., Gatt S. and Paturneau-Jouas M. (1984) Etude morphologique et biochimique de lipidoses induites et pathologiques dans des cellules musculaires en culture. Société Française de Recherche en Pédiatrie. Paris, France.

Morand O. and Aigrot M.S. (1984) Membrane-associated effects of inhibitors, trypsin and temperature on fatty acid transport across the membrane of human erythrocyte ghosts. XXVth International Conference on the Biochemistry of Lipids. Antwerpen, Belgium.

Morand O., Piciotti M. and Baumann N. (1983) Mechanism of fatty acid transport across biological membranes studied bu means of erythrocyte ghosts. XXIIIIth International Conference on the Biochemistry of Lipids. Toulouse, France.

Morand O., Fibach E., Livni N., Baumann N. and Gatt S. (1983) Induction of lipid accumulation in cultured cells by 12-(1-pyrene)dodecanoic acid. IXth Meeting of the International Society for Neurochemistry, Vancouver, Canada.

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DISSERTATIONS

Doctorat d'Etat Es-Sciences (Biologie et Génétique, Université Paris-VII, Octobre 1985). Etude des mécanismes de transport des acides gras au travers des membranes plasmiques.

Doctorat de 3ème Cycle (Nutrition, Université Paris VI, Janvier 1981). Sensibilité du cerveau en dévelopement aux facteurs exogènes: altération de la composition en acides gras de certains types cellulaires cérébraux provoquée par une malnutrition intra-utérine.

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